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Clinical picture

CLINICAL PICTURE

Juvenile diabetes and visual impairment: Wolfram syndrome

The presence of diabetes and visual impairment in a young individual is a good diagnostic criterion to suspect Wolfram syndrome (WS) or Diabetes insipidus, Diabetes mellitus, optic atrophy and deafness.[1,2] WS is a rare autosomal recessive disease due to mutations in the Wolframin (*WFS1*) gene. These mutations lead to endoplasmic reticulum stress-related decline of pancreatic beta-cell number and a decrease in endogenous insulin secretion. Affected individuals are therefore usually insulin-dependent, with a few rare exceptions reported.[3–5] Here we describe a 9-year-old boy who presented with visual impairment and diabetes, with a novel homozygous *WFS1* frameshift mutation p.(Ala671fs) confirming WS. This patient has a normal endogenous insulin level necessitating a very low total daily insulin requirement for good glycaemic control.

A 9-year-old boy presented to our endocrine clinic with decreased vision for 6 months and polyuria for 4 months. His parents were non-consanguineous and there was no family history of diabetes. His visual acuity was 1/6 on both eyes and retinal examination revealed bilateral optic atrophy without diabetic retinopathy (Figure 1A and B). His fasting blood glucose levels were elevated at 14.43 mmol/l with no ketonuria and HbA1C of 9.2%. Anti-glutamic acid decarboxylase antibody levels were normal with a normal c-peptide. An audiogram and an abdomen ultrasound were normal and there were no learning difficulties. An overnight water deprivation test was normal. In view of the optic atrophy and juvenile diabetes a genetic analysis was done to confirm WS. Sanger sequencing analysis of the *WFS1* gene (NM_006005.3) detected a homozygous frameshift mutation p.(Ala671fs), c.2010dup, in the last exon. This variant is predicted to result in insertion of a premature termination codon after 41 amino acids, resulting in possible translation of a truncated protein and loss of >10% of the normal WFS1 protein. The patient's parents were both heterozygous for the mutation. The patient was treated with small doses of insulin with remarkable glycaemic and visual improvement. He is currently requiring five units of biphasic insulin daily for the past 24 months with an HbA1c of 6% and no further neurodegenerative progression.

WS is a neuro-degenerative disorder due to mutations in the *WFS1* gene leading to non-autoimmune insulin-deficient diabetes mellitus. Due to the variable presentation there is no diagnostic marker available for this syndrome and, as in our case, juvenile diabetes with optic atrophy remain the best available clinical diagnostic criteria, even in the absence of other neurodegenerative features.[1,2] However, partial phenotypes in the absence of diabetes and optic atrophy have been previously described.[6] A possible genotype–phenotype relationship has been suggested, which could have implications for early diagnosis and management. Diabetic ketoacidosis and microvascular complications are seen less frequently in individuals with WS

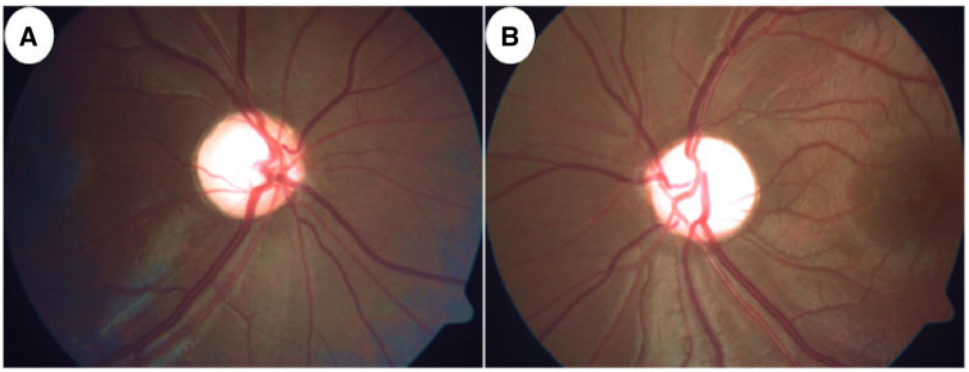

Figure 1. (A) Right eye retinal images showing optic atrophy without retinopathy. (B) Left eye retinal images showing optic atrophy without retinopathy.

than Type 1 diabetes.[5] Although it is common to have insulin deficiency, there have been a few reports similar to our case documenting an intact pancreatic reserve with normal c-peptide levels and very low insulin requirements.[3–5] Early identification with good glycaemic control in individuals with WS has been found to slow the progression of neuro-degenerative symptoms.[4] An association was found between HbA1c levels and neuro-degenerative syndromes and endocrine symptoms in WS.[4] Our patient is young and hence could progressively develop additional neurological features of WS later in life. However, poor glycaemic control and chronic hyperglycaemia is associated with a quicker progression of WS.[4] Our patient and larger series of subjects with WS need to be regularly monitored and followed up to promptly recognise progression, and confirm whether good glycaemic control results in a slower progression and better prognosis.

This case highlights the need for an increased vigilance towards early identification, genetic testing and treatment of WS in a young individual with visual symptoms and diabetes irrespective of the endogenous insulin reserve. A strict glycaemic control with a lower HbA1c target at follow up warrants a better quality of life with a slow progression of WS. Our case also illustrates the possible partial phenotypic presentation of this disorder confirming the variable spectrum of features at the time of presentation.

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